TESTIMONY OF DAVID P. HOLVECK

PRESIDENT AND CEO

CENTOCOR, INC.

BEFORE THE

COMMERCE COMMITTEE

SUBCOMMITTEE ON HEALTH AND ENVIRONMENT

UNITED STATES HOUSE OF REPRESENTATIVES

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Mr. Chairman members of the committee, I am David Holveck, President and Chief Executive Officer of Centocor, the largest biotechnology company in the state of Pennsylvania. We employ over 350 employees in the Philadelphia suburbs, and another 400 overseas. In addition, I serve on the Board of Directors of the Biotechnology Industry Organization. It is my pleasure to appear before you today to discuss issues related to the modernization of the Food and Drug Administration.

Central to this effort is the assurance of sufficient agency resources through both appropriated federal funds and user fees provided by the Prescription Drug User Fee Act or PDUFA. Passed in 1992, PDUFA has markedly shortened the time that it takes FDA to review new breakthrough biotechnology products. As the Committee is aware, PDUFA expires at the end of this fiscal year.

I would like to demonstrate to the committee the "real life" positive effect the user fee program has had on one biotech company involved in developing new therapies for heart disease, and in turn, on thousands of heart patients across this country. Currently, Centocor has one product on the market in the United States -- ReoPro -- indicated as an adjunct therapy for high risk balloon angioplasty patients. ReoPro is the first approved biologic in a new class of platelet inhibitor drugs. It works by effectively putting platelets to sleep in order to prevent the clotting which forms following balloon angioplasty. It is those clots which lead to heart attack, damaged heart tissue, and in some cases, death. ReoPro has shown dramatic clinical results, namely a 50% reduction in death and heart attack in the month following the angioplasty procedure. And, most dramatically, it has been proven to be a clinical benefit to patients lasting at least three years after just one administration.

ReoPro took over 10 years of clinical development from animal studies to the large scale trial which provided data for our FDA submission. And, it took just one year from submission to marketing clearance. The reason? The Prescription Drug User Fee Act of 1992. ReoPro was one of the first biotech products to see the benefits of the accountability and streamlining brought to the FDA through PDUFA. Over 120,000 patients have received ReoPro since launch of the drug in early 1995. Those patients, too,

saw the practical benefit of PDUFA by being given accelerated access to a new and innovative drug which, prior to PDUFA may have languished in the bureaucratic process.

I am convinced that ReoPro's short approval time was a direct benefit of the user fee program. Biotechnology is a leader in the war against disease and the products now available represent only the tip of the iceberg. There are approximately 284 biotechnology products currently in the FDA's pipeline for approval at various stages of testing. This represents a 21 percent increase from the year before. Any slowdown in the approval process will have dire effects on patients who suffer from serious and life-threatening diseases.

Last fall representatives from BIO, the PhRMA, and FDA initiated discussions on reauthorizing PDUFA. All parties felt that the success of PDUFA could be built upon to further improve agency efficiency. More importantly, it also provided an opportunity to explore how PDUFA funds could be used to shorten drug development. This is emerging as a critical issue as the ever-maturing biotechnology industry develops more products based on new cell, tissue, and gene therapies to treat a variety of serious and life-threatening diseases.

Through those discussions a series of performance enhancements were developed that could have a significant impact on drug development:

- **Electronic Filing of INDs and NDAs/BLAs**

  This promises to save industry millions of dollars in copying costs and document storage as submission of all documents from INDs to license applications will be by electronic means. Back to ReoPro, in 1993 it took over 50 volumes of data which filled a tractor trailer, for us to fulfill the requirements of our PLA filing. The FDA has already made strides in this area as now we are permitted to send individual case reports electronically.

I would encourage further use of electronic filing to save time and money not just for industry, but for the agency and its reviewers.

- **Meeting Management - Improving Predictability of Scheduling**

  Entitled meetings (pre-IND, end of Phase II, and pre-NDA/BLA) would be scheduled and held within 60 days of the sponsor's request. A new category of critical meetings (where development would be halted unless a crucial issue is resolved) will be held within 30 days of request. All other meetings would be held within 75 days of request. Minutes, outlining important agreements, disagreements, and issues for further discussion, would be provided to the sponsor 30 days after the meeting. This would provide a more "user-friendly" atmosphere for both industry and the FDA.

- **Clinical Holds - Reducing Response Time**

  It is reasonable that FDA will respond within 30 days of receipt of the sponsor's complete response to issues raised in the clinical hold.

- **Written Protocol Agreements - Establishing a Record of Agreements on Protocol Design**

  FDA would make a decision within 45 days of a sponsor's submission for review of a research protocol. Any agreements on the design, execution, and analyses proposed in protocols reviewed under this provision would not be altered unless public health risks unrecognized at the time of protocol assessment are evident.

  Appeals Process - Predictable Resolution of Disagreements.

  A two tier process has been designed to resolve disputes between sponsors and FDA reviewing Divisions. The first level of appeal will be with the Office

Director. The second level will be the Center Director (or Deputy). At each level, FDA will respond within 30 days of submission. In certain instances the issue may be presented to an advisory committee. If there are not 30 days before the next scheduled advisory committee, the issue will be presented at the next scheduled meeting to conform with administrative procedures.

- **Simplification of Application Letters and Notification of Deficiencies - Shortening Recycle Times**

  FDA will discontinue the use of non-approvable letters. These letters have caused difficulty for biotechnology firms in capital markets. Receipt has been perceived as rejection of the application with resultant drop in stock price despite the fact that several products were approved following resubmission. If the sponsor does not receive an approval at the end of the review period a "complete response" (CR) would be sent detailing the specific deficiencies and the actions necessary to place the application in condition for approval. Sponsors will also be notified of deficiencies following the review of sections of the application. These "information request" (IR) letters will allow the sponsor to begin responding to deficiencies as quickly as possible. Resubmissions will fall into two classes. Those falling into Class I require a shorter period of time and FDA will act upon these in two months. Class II includes items such as a major reanalysis of the data or new clinical trial information and will continue to be reviewed within the current six month time frame.

- Faster Reviews and Use of Third Parties - Improving Efficiency

  Under PDUFA-II, standard review times would come down from 12 to 10 months, Manufacturing supplements will be reduced from six to four months. FDA will be permitted to use PDUFA funds to contract out reviews to meet user fee performance goals.

Collectively, if enacted, these enhancements will shorten drug development times by 10-16 months improving patient access to new therapies.

One other key issue proposed by BIO during the PDUFA discussion was to improve the manner by which manufacturing changes have been handled. Many times companies seek to improve the manufacturing process following approval. In the past virtually all manufacturing changes for biotechnology products required pre-approval by FDA.

This is changing for the better as FDA is in the process of finalizing a new regulation, However, much more remains to be done. We need to have a flexible approach where changes to the process that do not affect the purity or quality of the drug can be readily implemented.

Another issue that Centocor views as important is the dissemination of scientifically accurate information to physicians. Experts in the field should have access to peer-reviewed publications, otherwise clinical science will always be two steps behind reality. In addition, we have entered a new era of managed care and it is important that companies such as Centocor can deal directly with the various organizations that have emerged to provide them with timely information to improve patient outcomes and reduce health care costs. Pharmacoeconomic information is sometimes produced following initial

approval, and that data could have a direct impact on how the product fits in with the health care economy. Each of these matters needs to be addressed and a better mechanism developed aside from present FDA pre-approval requirements. Please do not leave the dissemination of information issue off the table simply because of its complex and controversial nature.

Let me also say that the biotech and drug industries have raised not just a few eyebrows by coming to Capitol Hill in favor of user fees. Yet, as I hope I've illustrated with my example of our product ReoPro, the user fee program works. But it only works because the fees have been tied directly to accountability of the agency. Proposals to implement unauthorized user fees on other industries into the general fund budget of FDA are dead wrong. This program needs full congressional support of its original intent, and must not be used as a tool to shortchange the FDA budget.

In conclusion, I would urge the reauthorization of PDUFA for a full five years along with other mainstream provisions that will improve FDA's ability to approve breakthrough products in an expeditious manner. The biotech industry already entails some risk, and a one-year extension of PDUFA does not provide the long-term security and stability that the investment community and patient community need to renew their confidence in our industry. As I just mentioned, it is important that FDA receive sufficient funding so that the additive PDUFA funds can implement the performance enhancements that industry and FDA have identified.

We also support, as Mr. Binder discussed in his testimony, efforts to modernize the agency. We look forward to working with you on these matters.

Thank you for your time today, and I would be happy to answer any questions you may have.